

Horizontal bone grafting using equine-derived cancellous bone blocks is associated with severe complications: A prospective clinical and histological pilot study

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Abstract

Aims: The aim of this prospective, clinical study was to evaluate the clinical performance and histological outcome of a new equine hydroxyapatite collagenated bone block (eHAC) for horizontal bone grafting prior to implant placement.

Materials and Methods: Five patients (two male/three female) with a mean age of 51.6 years (range 22–66 years) and a reduced horizontal bone width of the alveolar ridge (mean 3.5 mm) underwent horizontal bone grafting using eHAC at 10 grafting sites. Reentry was performed 6.9 months after the horizontal grafting procedure. Clinical follow-up (mean 28.9 month) considered width gain of the alveolar ridge, soft tissue healing, and complications. To evaluate graft incorporation, four additional patients underwent histological assessment of equine blocks adjacent to autologous blocks 3 and 6 months after grafting.

Results: The study was terminated after graft failure was observed in four of five patients. Mean horizontal bone width had increased by 3.6 ± 1.22 mm. Three out of nine implants placed had to be removed due to graft failure. Histological evaluation revealed large amounts of soft connective tissue within the grafts (mean $67.3 \pm 9.5\%$). The proportion of new bone formation 3 months after the lateral grafting procedure revealed an average of 8.6%, compared to 11.4% after 6 to 7 months.

Conclusion: Lateral ridge grafting using eHAC achieved measurable horizontal width gain but revealed high rates of severe complications.

Clinical Implications: Within the limitations of this study, eHAC bone blocks cannot be recommended for horizontal bone grafting.

KEYWORDS

alveolar ridge grafting, augmentation, clinical trial, dental implants, equine bone, histology

Andres Stricker and Tobias Fretwurst contributed equally

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1 | INTRODUCTION

To achieve long-term implant stability, a sufficient alveolar bone volume is mandatory. In atrophic jaws, vertical and horizontal bone grafting procedures are required prior to implant placement to enable an adequate three-dimensional implant position (Sanz & Vignoletti, 2015). Autologous bone is still considered to be the gold standard in alveolar defects > 5 mm because of its transplant competence, mainly used as block grafts (Fretwurst, Gad, Nelson, & Schmelzeisen, 2015; Fretwurst, Nack, et al., 2015; Fretwurst, Wanner, et al., 2015; Jensen & Terheyden, 2009; Sanz-Sanchez, Ortiz-Vigon, Sanz-Martin, Figuero, & Sanz, 2015). However, a disadvantage is the associated donor site morbidity (Cordaro, Torsello, Miuccio, di Torresanto, & Eliopoulos, 2011; Cremonini, Dumas, Pannuti, Lima, & Cavalcanti, 2010; Fretwurst, Nack, et al., 2015; Fretwurst, Wanner, et al., 2015; Nkenke et al., 2002; Nkenke, Schultze-Mosgau, Radespiel-Troger, Kloss, & Neukam, 2001). Therefore, allogeneic and xenogeneic bone substitutes are considered for clinical application. Xenogeneic grafts are primarily of bovine, porcine, or equine origin. In implant dentistry, equine hydroxyapatite collagenated cancellous bone blocks containing endogenous collagen type I and III (eHAC; Bio-Graft™, Geistlich Pharma AG) and equine femur bone (Osteopant®, OsteOXenon, Bioteck), an enzyme deantigenized cortical and/or cancellous bone block with a preserved type I collagen component are available for application. In preclinical studies in rats, dogs and primates equine bone blocks demonstrated complication rates of up to 20% (soft tissue dehiscences) and a low rate of new bone formation (6%) compared to autologous (19%) grafts after 1 month of healing (Benic et al., 2016, 2017; Fontana, Rocchietta, Dellavia, Nevins, & Simion, 2008; Nevins, Al Hezaimi, Schubach, Karimbux, & Kim, 2012; Schwarz et al., 2010; Simion et al., 2009; Zecha et al., 2011).

Four clinical human studies using equine bone blocks (Osteopant® and eHAC) for horizontal bone grafting demonstrated a horizontal gain of 3–4 mm (Di Stefano et al., 2009; Ortiz-Vigon et al., 2018; Pistilli et al., 2014; Schwarz, Mihatovic, Ghanaati, & Becker, 2017). However, in two studies using eHAC bone blocks a rate of 70% of soft tissue dehiscence was reported (Schwarz et al., 2017), and Ortiz-Vigon et al. (2018) noted an accumulation of complications such as soft tissue dehiscences (35.7%) and an high incidence of implant loss (30.8%).

Histological evaluation was performed in three clinical studies 24 to 26 weeks after horizontal bone grafting (Di Stefano et al., 2009; Ortiz-Vigon, Martinez-Villa, Suarez, Vignoletti, & Sanz, 2017; Schwarz et al., 2017). Using vertical core biopsies, Schwarz et al. found remnants of eHAC in 3 of 8 biopsies but histomorphometric evaluation was not performed. Ortiz-Vigon et al. (2017) also performed vertical biopsies of the grafted alveolar regions in 13 patients and revealed a mean of 26.9% of vital bone and 24.4% of eHAC remnants. However, vertical biopsies retrieved at the site of implant placement usually include residual alveolar bone and parts of the block graft and therefore may not allow a full evaluation of the block revascularization. Only Di Stefano et al. used a horizontal

technique to harvest 5 biopsies after horizontal bone grafting with an Osteopant® bone block and a titanium reinforced, expanded polytetrafluoroethylene membrane (W.L. Gore & Associates®). The authors demonstrated 35% newly formed bone and 30% residual grafting material (Di Stefano et al., 2009).

There is a lack of data concerning the clinical performance and histological outcome of eHAC for horizontal bone grafting in human alveolar bone defects. Therefore, the aim of the present prospective clinical study was to evaluate the clinical performance and histological outcome of eHAC for horizontal bone grafting using horizontal biopsies.

2 | MATERIAL AND METHODS

2.1 | Study design

This study was designed as a prospective clinical pilot study, to assess the performance of eHAC bone grafts (Bio-Graft™, Geistlich Pharma AG) for horizontal bone grafting prior to implant placement. The study was conducted at two centers, Department of Oral and Maxillofacial Surgery, University of Freiburg and the Center of Implantology, Periodontology and 3D Head-and-Neck Imaging Lake Constance. The number of patients planned to include was 16. All patients were treated in accordance with the Helsinki Declaration of 1964, as revised in 2013. All patients had to sign an informed consent statement. The study was approved by the ethics committee of the University medical center of Freiburg (no. 503/13). The clinical procedure and monitoring protocol was examined and confirmed following the GCP guidelines (ISO 14155:2011) and STROBE criteria (see Appendix S1). The study recruitment phase was 12 months starting from February 2014 to February 2015. Follow-up was performed until 2019. A graft failure rate > 30% was defined as termination criterion in the study protocol.

2.2 | Patient sample

Patients with lateral ridge defects were included in the study. Inclusion criteria were as follows: a minimum age of 18 years and defined defects for horizontal bone augmentation with sufficient bone height but insufficient alveolar bone width at the recipient site for implant placement and a healthy attached oral mucosa of at least 3 mm height.

Exclusion criteria comprised general prohibitive conditions for dental and/or surgical treatments, including thin mucosa biotype (<1 mm), diabetes, a history of malignancies requiring chemotherapy or radiotherapy within the past 5 years, radiotherapy of head and neck area, immunosuppressive and antiresorptive therapy. Smokers, pregnant, or lactating women and patients who participated in an investigational device, drug, or biologics study within the 24 weeks prior to the start of the study were also excluded.

2.3 | Surgical phase, follow-up, and clinical measurements

Bone grafting was performed in local anesthesia with UDS forte (Sanofi Aventis) using a crestal incision with a vertical releasing incision distally if necessary to elevate a full-thickness flap. After inspection of the alveolar defect, the recipient bone was preconditioned by perforation and decortication. The eHAC blocks were trimmed, adjusted to the defect size and after predrilling, fixated with recommended osteosynthesis screws (Osteosynthesis screws, Geistlich Pharma AG).

Contouring of the graft using deproteinized bovine bone mineral DBBM (BioOss®, Geistlich Pharma AG) was performed as a resorption protection of the cancellous equine grafts as described for bone grafting procedures with bone blocks from the iliac crest (Wiltfang et al., 2014). The graft was covered with a resorbable collagen membrane (Bio-Gide®, Geistlich Pharma AG).

Periosteal releasing incisions were performed to accomplish a tension-free closure using absorbable continuous sutures (Monocryl 5-0, Ethicon). Standard post-surgical medication, consisting of 600 mg of Ibuprofen (2/d) and either 750 mg of amoxicillin (3/d) or clindamycin 600 mg (3/d), was prescribed. Suture removal was scheduled after 2 weeks.

Photo documentation and assessment of the alveolar ridge width were measured before and after surgical augmentation and during reentry using a caliper and a periodontal probe at defined points which were chosen in relation to the adjacent teeth in order to ensure reproducibility. Clinical inspection was performed due to a standardized follow-up protocol: 1, 14 days, 4 and 13 weeks after augmentation. At reentry, 7 months after grafting procedure implant placement was performed.

Clinical performance of the equine grafts was described. Complications such as infections or pain and presence of soft tissue dehiscences as well as removal of graft or implants were documented.

2.4 | Histological analysis

Four additional patients received lateral alveolar crest grafting using eHAC adjacent to autologous blocks for histological assessment.

Histological biopsies were harvested 3 to 7 months (2 samples after 3 months, 3 samples after 6 months, and one sample after 7 months) after grafting using horizontal trephines with a diameter of 1.7 mm (Helmut Zepf GmbH) (Figure 1). In total, six biopsies were retrieved. All

biopsies were fixed in 4% formalin for 7 days and stepwise dehydrated in an ascending solution of ethanol (70%, 80%, 90%, 100%), remaining in each concentration for 24 hr. Specimens were then degreased in xylene (Merck) for 1 day, infiltrated, embedded, and polymerized in methylmethacrylate (Merck) (Richardson, Jarett, & Finke, 1960). Using a precision cutting machine Secotom 50 (Struers), samples were sliced in 600 µm sections and mounted onto acrylic slides (Maertin). Sections were then ground to a thickness of 100 µm using a rotating grinding plate (Struers). Staining was performed with pararosaniline (Sigma, Merck) and azure II (Merck) (Jeno & Geza, 1975). For imaging, an Axio Imager M1 microscope equipped with a digital AxioCam HRC (Carl Zeiss) was used. Samples were histomorphometrically evaluated. Relative proportions of bone, biomaterial, and connective tissue were identified and quantitatively evaluated using the imaging software for Life Science Microscopy analysis (OLYMPUS EUROPA GmbH). The amount of mineralized and non-mineralized structures within the graft was assessed. The mineralized structure was further divided into graft components and newly formed bone.

2.5 | Statistical analysis

The software package (IBM SPSS Statistics 21.0; IBM Corporation) was used for the descriptive analysis. The variables graft survival, implant survival, and bone volume changes were analyzed. A dependent *t* test was performed for parametrically distributed data, while a Wilcoxon test was applied for nonparametrically distributed data. The significance level was set at $p \leq .05$.

3 | RESULTS

3.1 | Clinical performance

Five patients (two males/three females) with a mean age of 51.6 years (range 22–66 years) and a reduced horizontal bone height of the alveolar ridge (mean 3.5 mm) underwent horizontal bone grafting using eHAC at 10 grafting sites. Every eligible patient asked to participate and agreed to participate in the study. Patient data are summarized in Table 1. For histological analysis, four additional patients received horizontal bone grafting using eHAC mesial and/or distal to an autologous bone block graft. Recruitment was terminated after 30% of the grafts failed.

FIGURE 1 Horizontal histological biopsies. Lateral alveolar crest grafting was performed with eHAC adjacent to autologous bone grafts (a). Horizontal sample harvesting was performed with a trephine 3 and 6 months after grafting (b). Notice the resorbed eHAC graft in comparison to the autologous grafts

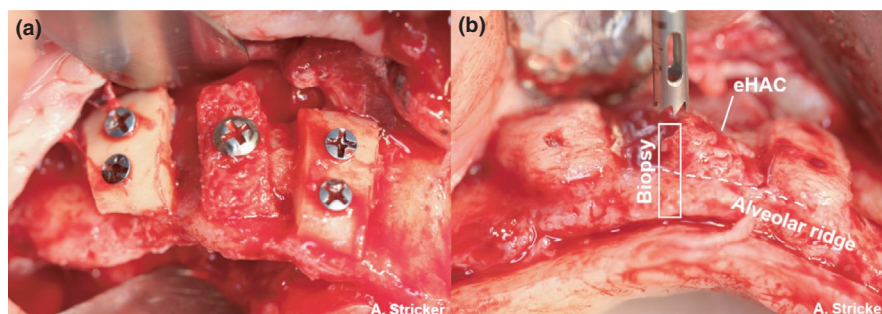


TABLE 1 Patients data and overview of complications

Patient	Gender	Age [years]	Grafting site [region]	Reentry [months]	Implant type	Complications	Complication [months ^a]	Last follow-up [months ^a]
1	F	59	45, 46 36	7	2 × Camlog RootLine Ø 3.8 × 11 mm	Removal of graft and implants	10	34
				7	Camlog ScrewLine Ø 3.8 × 9 mm	–	–	34
2	F	48	11	7	Straumann BL Ø 4.1 × 10 mm	Removal of graft and implant	13	22
3	F	63	36 46, 47	7	BioMet 3i BOPT Ø 4.0 × 10 mm	Soft tissue dehiscence	9	19
				7	2 × BioMet 3i BOPT Ø 4.0 × 10 mm	Soft tissue dehiscence Removal of graft	9 18	19
4	M	22	44, 45	6	2 × Camlog ScrewLine Ø 3.8 × 11 mm	–	–	56
5	M	66	35	7	–	Removal of graft	7	18
5 patients	2 M, 3 F	Ø 51.6 years	10 grafting sites	Ø 6.9 months	9 implants placed 6 successful, 3 removed	60% graft failure	Ø 11 months	Ø 28.9 months

Note: The study was terminated after graft failure in 60% of the grafted sites and removal of three implants (33%).

^aMonths after grafting.

During the grafting procedure, the surgical handling of the equine bone blocks demonstrated initial problems, as seven blocks in four patients cracked during fixation using the recommended osteosynthesis screws. These grafts were not placed and new eHACs were fixed. Before grafting, the alveolar crest showed a horizontal ridge width of 3.5 ± 0.7 mm (Table 2). All grafting procedures were completed successfully. None of the five patients reported pain after the surgery and no signs of inflammation or soft tissue dehiscences were assessed during follow-up. All patients continued the follow-up until scheduled reentry after 6.9 months (range 6–7 months).

At reentry, 9 of 10 sites showed sufficient alveolar ridge width for implant placement. One graft demonstrated insufficient stability and had to be removed. In this patient, a second grafting procedure using an autologous bone block lead to successful implant placement after 3 months. The mean ridge width at implant placement was 7.1 ± 0.9 mm, leading to a mean horizontal width increase of 3.6 ± 1.2 mm. In total, nine implants (Camlog, Straumann, BioMed) were placed in four of five patients (Table 1).

After implant placement, no further graft or implant was lost until prosthetic loading.

3.2 | Complications

6 of 10 grafting sites (60% of all grafts) failed, and three out of nine implants had to be removed (33% implant failure rate).

In one patient, 8 months after prosthetic rehabilitation (18 months after grafting) a sequester occurred at the site of grafting (Figure 2). Three grafting sites demonstrated graft exposure 10 and 13 months after grafting resulting in the removal of the grafts together with the implants. Only one patient demonstrated no grafting or implant failure within the observation period of 56 months after grafting (Figure 3).

3.3 | Histological analysis

3.3.1 | Native equine bone block prior to grafting

The low power magnification depicts trabecular bone structures in the equine bone blocks prior to grafting (Figure 4a). At higher magnification, the analyzed equine bone blocks showed organic material consisting of cells and cell debris that varied in type and number. Remnants of osteocytes and adipocytes in many intertrabecular segments of the sample were detectable (Figure 4b, c).

3.3.2 | Histomorphometry 3–6 months after grafting

Histological and histomorphometric evaluation revealed large proportions of non-differentiated dense fibrous tissue with high amounts of lymphocytes 3 months after grafting (Figure 5a, b). Islands of new bone formation on the trabeculae were visible. The

TABLE 2 Grafting sites and alveolar ridge volume

Patient	Grafting site [region]	Number of blocks	Ridge width at baseline [mm]	Ridge width at reentry [mm]	Gain in ridge width [mm]
1	45	2	4	8	4
	46		4.5	8	3.5
	36	1	4	No measurement	-
2	11	1	3	6	3
3	36	1	4	6	2
			4	6	2
	46	2	4	7	3
	47		3	8	5
4	44	1	2	7	5
	45		3	8	5
5	35	1	3	Block removal	-
	10	9	3.5 (SD 0.7)	7.1 (SD 0.9)	3.6 (SD 1.2)

Note: Alveolar crest volume changes were evaluated clinically at reentry. Alveolar ridge width at baseline was 3.5 ± 0.7 and 7.1 ± 0.9 mm after grafting. Mean horizontal bone width increased by 3.6 ± 1.2 mm.

mean amount of new bone formation was 8.6% (range: 4%–13%) after 3 months (Table 3). Adjacent to the trabeculae surface multinucleated cells were detectable (Figure 5c).

After 6 months, differentiated bone marrow with vessels and adipocytes (Figure 6) was visible, with new bone formation adjacent to the trabecular surface (mean new bone formation 11.6%, range: 1.6%–22%) and howship lacunae on the bone surface (Figure 6b). However, two samples demonstrated minimal new bone formation even after 6 months (Figure 6d, e). In all samples, new bone formation is initiated from the residual alveolar ridge and decreases laterally.

4 | DISCUSSION

The present prospective clinical and histomorphometric pilot study was conducted to evaluate the clinical applicability and performance of eHAC for horizontal bone grafting. The study was terminated after graft failure in 80% of the patients and an implant failure rate of 33%.

The results are similar to the data of Ortiz-Vigon et al. (2018) demonstrating an implant failure rate of 30.8% after eHAC grafting. In contrast to the present study, a high rate of 30% early soft tissue dehiscence immediately after grafting was described by Ortiz-Vigon et al. (2018) and of 70% by Schwarz et al. (2017). Even though a high rate of soft tissue dehiscence was reported by Schwarz et al. (2017), no graft or implant failure was observed probably due to smaller initial defect size and the selected defect configurations, as only single tooth gaps were included in comparison with the major horizontal defects restored in the study of Ortiz-Vigon et al. (2018) and in the present study. The defect configuration in single tooth gaps, which is rather self-containing might influence the graft remodeling and incorporation (Elnayef et al., 2018). Nevertheless, in the study of Schwarz et al. (2017), at implant placement an additional

grafting procedure, respectively, contour augmentation due to an insufficient horizontal ridge was indicated in 40% of the patients. Equine blocks from a different supplier (Osteopant®, OsteOXenon, Bioteck) demonstrated an eHAC-comparable incidence of graft failures (50%) and implant loss (20%) in a randomized controlled clinical trial including 40 patients (autologous bone as control: 0% graft failures) (Pistilli et al., 2014).

Neglecting the high rate of graft and implant failure of equine bone blocks, 7 months after grafting the mean horizontal bone volume increased by 3–4 mm. These values are comparable with those of intraoral harvested autologous blocks after 6 months (3.9 ± 0.38 mm) (Sanz-Sanchez et al., 2015). Although the initial horizontal gain of bone volume after equine block grafting is promising, long-term data on the stability and resorption properties of the equine cancellous bone are lacking. To analyze graft incorporation and new bone formation, histological examination of equine grafts was performed 3 to 7 months after horizontal bone grafting. In general, vertical biopsies are obtained at the implant site which is the preferred approach to illustrate the quality of bone at the implant surface. However, this does not allow evaluation of the graft remodeling. Horizontal biopsies allow a discrimination of graft and residual bone and the evaluation of the remodeling throughout the complete graft. If the biopsy remains in the trephine bur, the sample remains intact and allows spatial orientation within the sample. Hence, in the present study horizontal trephine biopsies were obtained and histomorphometric analysis revealed a trabecular structure of the graft with large proportions of soft tissue (69.7%) within the grafted areas after 3 months and 66.2% after 6 to 7 months. The mean amount of new bone formation was 8.6% after 3 months and 11.4% after 6 to 7 months. In comparison, Ortiz-Vigon et al. (2017) reported $47.1 \pm 19.2\%$ of soft tissue proportion and $26.9 \pm 12.2\%$ of new bone formation within the vertical biopsies. As mentioned earlier, the mode of biopsy retrieval could influence the amount of bone, as

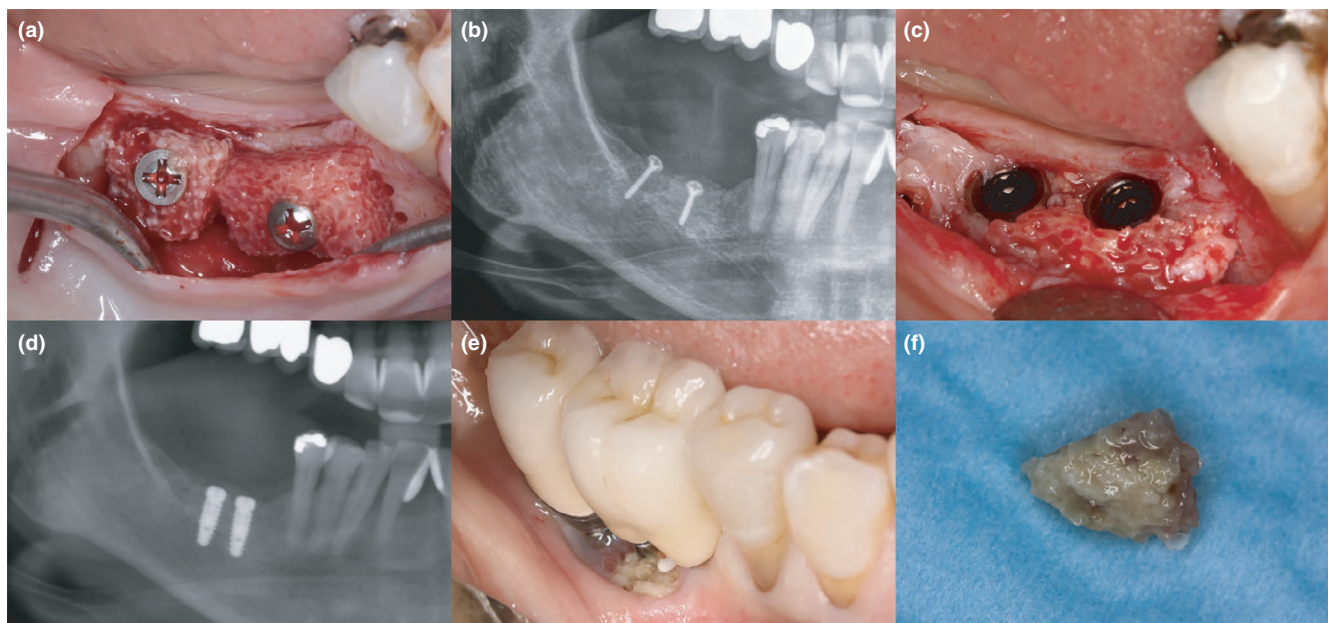


FIGURE 2 Late dehiscence of eHAC after prosthetic restoration. After grafting procedure, implant placement could be performed at 7 months (2 × BioMet implants). During further observation, a late dehiscence occurred 18 months after grafting procedure. As a consequence, the two grafts were removed

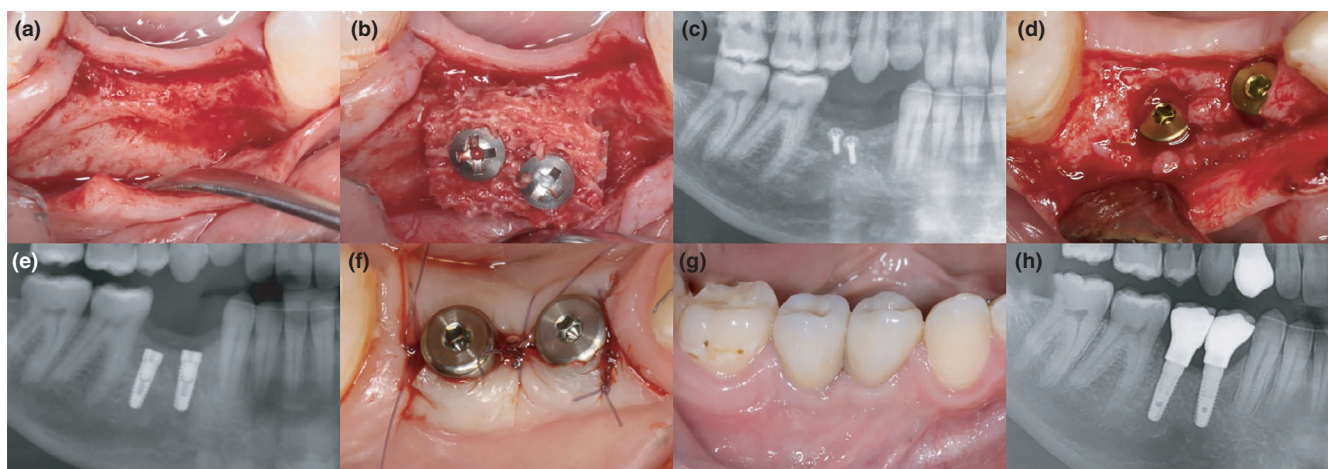


FIGURE 3 Successful lateral alveolar crest grafting using eHAC in a 22-year-old patient. Reentry 6 months after grafting demonstrated sufficient alveolar ridge width for implant placement of two implants (2 × Camlog ScrewLine 3.8 × 11 mm). Second stage surgery and prosthetic restoration were performed after grafting procedure. The last follow-up was performed 56 months after grafting

parts of the residual bone might have been captured within the sample. Since Schwarz et al. (2017) did not perform histomorphometry, no conclusions or comparison can be drawn. In the present study, histological evaluation revealed large proportions of non-differentiated dense fibrous tissue with high amounts of lymphocytes and isolated multinucleated cells on the trabeculae of the graft after 3 months. Fibrous ingrowth during the healing process might have prevented bone formation in some cases. However, all grafting procedures were conducted using a cell occlusive collagen membrane (Bio-Gide®, Geistlich Pharma AG) as specified in the study protocol. Animal studies investigating eHAC bone grafting question the need

for a barrier membrane to promote bone ingrowth, since no histological difference concerning new bone formation and graft incorporation with and without collagen membranes was demonstrated (Simion et al., 2009; Zecha et al., 2011).

A graft failure rate of 60% as demonstrated in the present study is unacceptable in daily clinics, as alveolar reconstruction using particulate bovine bone and autologous bone as block or shield demonstrates low complication rates and long-term stability (Fretwurst, Nack, et al., 2015; Fretwurst, Wanner, et al., 2015; Troeltzsch et al., 2016). Since no soft tissue dehiscences occurred in the present study, possible graft failure mechanisms could be attributed to insufficient graft

FIGURE 4 Histological section of an equine block prior grafting (staining azure 2 and pararosaniline). (a) Overall view. (b) magnification $\times 100$ (arrows indicating adipocytes). (c) magnification $\times 400$ (arrows indicating osteocytes)

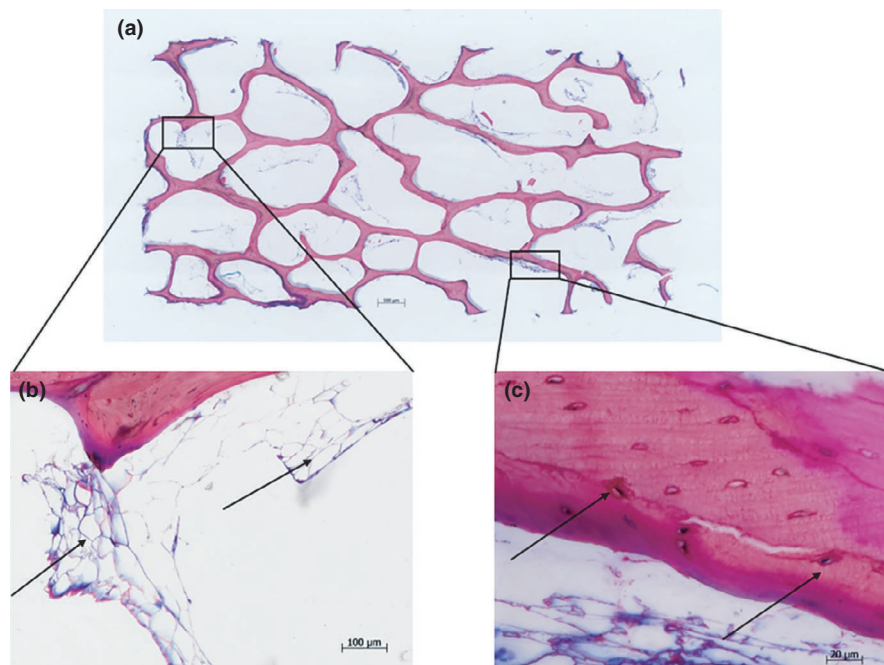


FIGURE 5 Histological analysis of an equine block 3 months after grafting (staining azure 2 and pararosaniline). (a) Overall view. (b) Non-differentiated dense fibrous tissue with high amounts of lymphocytes adjacent to the trabeculae. (c) Arrow is indicating a multinucleated cell

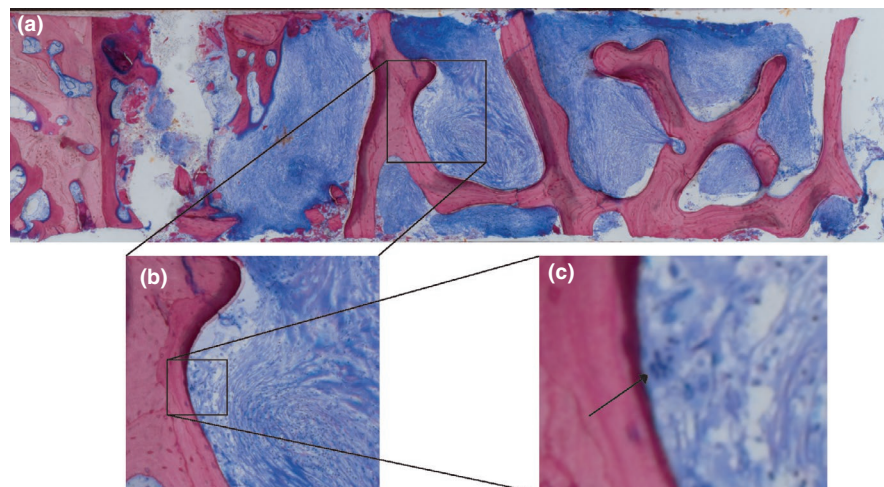


TABLE 3 Histomorphometric analysis of the biopsies

Patient	Biopsy [region]	Reentry [months]	Soft tissue [%]	Mineralized fraction [%]	eHAC [%]	New bone formation [%]
6	35	3	66.5	33.5	29.1	4.4
7	13	3	72.8	27.2	14.4	12.8
	23 basal	6	62	38	24.2	13.8
	23 coronal	6	78.4	21.6	13.3	8.3
8	24	6	72.6	27.4	25.8	1.6
9	17	7	51.8	48.2	26.4	21.8

Note: Six biopsies were harvested after 3 to 7 months. After histological preparation, histomorphometric evaluation was performed. The biopsies showed high proportions of soft tissue (mean $67.3 \pm 9.5\%$). New bone formation was 8.6% at 3 months and 11.4% at 6 to 7 months.

incorporation/remodeling due to a low transplant competence (poor osteoconductive properties), graft infection after implant placement and/or remaining equine cell and protein content with a possible corresponding immunogenic potential. The latter is supported by

histological evaluation of native blocks prior grafting which revealed organic material such as cells and cell debris within the graft trabeculae (Figure 4). Interestingly, a current review summarizing the literature of allogeneic, cancellous bone blocks for vertical bone grafting

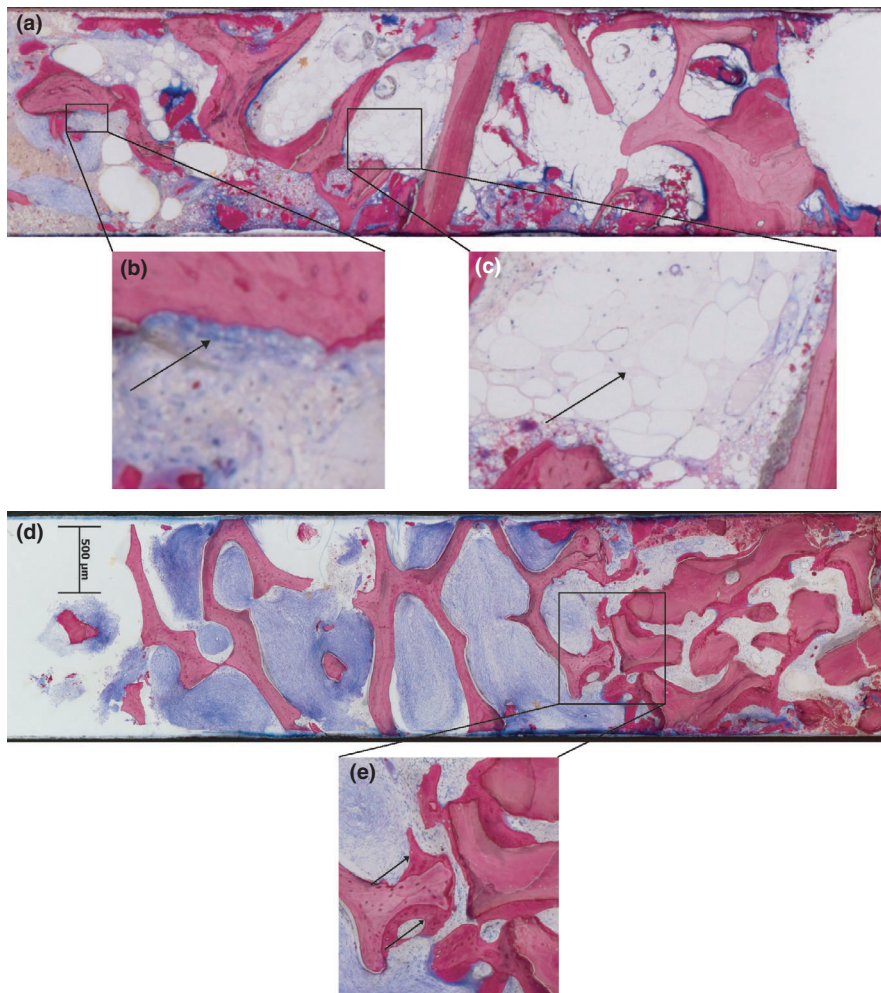


FIGURE 6 Histological analysis of two equine bone blocks 6 months after grafting (staining azure 2 and pararosaniline). (a) Overall view of a bone block with differentiated bone marrow and a rate of 8.3% of new bone formation. (b) Howship lacunae (arrow). (c) Bone marrow with vessels and adipocytes (arrow). (d) Overall view of a bone block with a low rate of new bone formation (1.6%) after 6 months of healing. (e) Dense soft tissue and minimal new bone formation originating from the residual alveolar bone (arrows)

reported severe complications with similar delayed graft and implant loss after implant placement and prosthetic loading like in the present study, which makes a similar failure mechanism conceivable (Draenert, Kammerer, Berthold, & Neff, 2016). An immunological reaction to major histocompatibility complex molecules of remaining cells has not been described for equine grafting materials yet. Although it is known that horse gene sequences showed homology to DNA sequences in the human genome, the impact of remaining cells and proteins on host immune response or induction of a foreign body reaction has not been examined (Tozaki et al., 2007). Processing of equine bone blocks is based on hydrolytic enzymes to dissolve and eliminate immunogenic components such as cells, proteins, and lipids from the tissue and preserve bone cell adhesion and remodeling properties (Cusinato et al., 2016). However, the mechanism for the late failure of the equine bone grafts and the small rate of new bone formation is still unclear and could be investigated with regard to the immunogenic and architectural properties of the blocks in future studies.

4.1 | Limitations

The conclusions of this prospective clinical and histological study are limited due to the lack of a control group and a small sample

population. This arises from ethical considerations to terminate the study after a high rate of late graft failures.

5 | CONCLUSION

The clinical application of eHAC for horizontal bone grafting revealed a high occurrence of complications including late soft tissue dehiscences, graft failure, and implant loss. Within the limitations of this study, eHAC bone blocks cannot be recommended for horizontal bone grafting.

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CONFLICT OF INTEREST

The authors do not have any financial interest, either directly or indirectly, in the products listed in the paper. The investigation was sponsored by Geistlich Pharma AG.

AUTHOR CONTRIBUTIONS

Johannes Angermair: Data curation (equal); Formal analysis (equal); Investigation (equal); Project administration (equal); Supervision

(equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Dieter D Bosshardt:** Formal analysis (equal); Investigation (equal); Visualization (equal); Writing-original draft (equal). **Katja Nelson:** Conceptualization (lead); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Tabea Flügge:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal). **Andres Stricker:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Validation (equal); Visualization (equal). **Tobias Fretwurst:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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